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ORIGINAL ARTICLE

Sesquiterpenoids from the Rhizomes of *Homalomena occulta*

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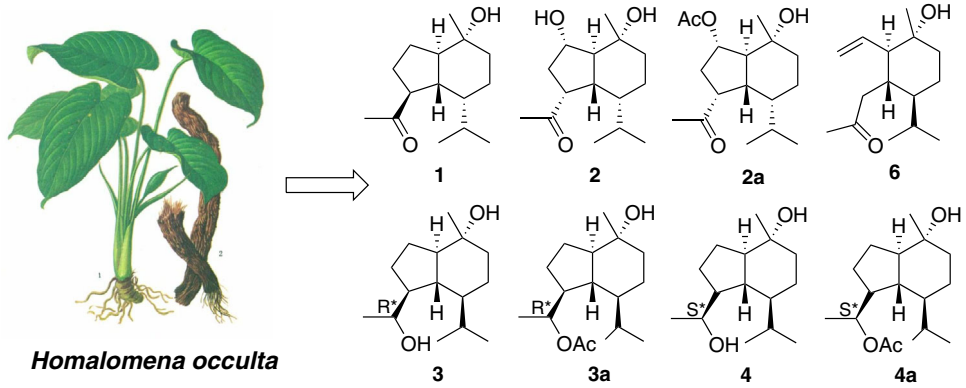
Abstract Naturally occurring oplopanane sesquiterpenoids are rarely reported. A phytochemical investigation on the rhizomes of *Homalomena occulta* (Lours) has resulted in the discovery of six oplopanane sesquiterpenoids (**1**–**6**), including four new (**1**–**4**) and one 3,5-*seco*-oplopanane (**6**), together with three previously reported sesquiterpenoids (**7**−**9**). In addition three new oplopananes (**2a**–**4a**) were also obtained by chemical transformation. All structures of these sesquiterpenoids were established based on the comprehensive spectroscopic analyses, including NMR, MS, and IR, and comparing with the literatures.

Graphical Abstract



Keywords *Homalomena occulta* · Sesquiterpenoids · Oplopananes

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1 Introduction

With its rich cultural heritage and biodiversity, traditional Chinese medicine (TCM) has potential as a source for the discovery of structurally novel bioactive compounds. During the last twenty years, considerable efforts have been dedicated towards the exploration of the natural product chemistry of TCM. *Homalomena occulta* (Lour.) was officially listed in the Chinese Pharmacopoeia (named Qian-nian-jian) [1], and was found to occur in the tropical and sub-tropical areas of Asia and America. The plant has

been used for the treatment of rheumatoid arthritis, trengthening tendons and bones, and invigorating the kidney and liver [2, 3]. Recent reports of *H. occulta* have also shown that the species is one of the most prolific sources of compounds with new structures [2–6].

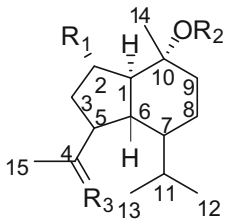
Our research group has considerably focused on phytochemical investigations of TCM [7–10]. As part of our continuing efforts to obtain novel compounds with exquisite structural architectures, we initiated a chemical investigation of *H. occulta*, which has thus far led to the isolation and structural elucidation of six oplopanane sesquiterpenoids (**1–6**), including four new (**1–4**) and one 3,5-*seco*-oplopanane (**6**), together with three previously reported sesquiterpenoids (**7**−**9**).

2 Results and Discussion

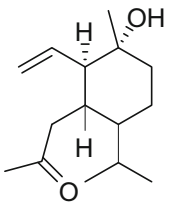
By means of diverse chromatographic methods, including silica gel and LH-20, four new oplopanane sesquiterpenoids (**1**−**4**) (Fig. 1) have been purified from an 88 % ethanol/water extract of the rhizomes of *H. occulta*.

Compound **1** was isolated as an optically active colorless oil with $[\alpha]_D^{20}$ –54 (*c* 0.07, $CHCl_3$). Its molecular formula was analyzed as same as oplopanone (**5**) [11], i.e. $C_{15}H_{26}O_2$, based on a pseudomolecular ion peak at *m/z* 256.2272 $[M + NH_4]^+$ (calcd. 256.2271) in the positive HRESIMS spectrum, indicating three degrees of unsaturation. The IR absorptions suggested the existence of hydroxy (3382 cm^{-1}) and ketone (1705 cm^{-1}) functionalities. The ^{13}C NMR spectra (Table 1) showed the presence of one oxygenated quaternary carbon (δ_C 73.2) and one ketone carbon (δ_C 212.3). Overall NMR pattern, together with the established molecular formula, showed close resemblance to those of oplopanone (**5**) [11], which indicated that compounds **1** and **5** were possibly epimers of each other. The large coupling constants of $J_{H\text{-}1,H\text{-}6}$ (12.0 Hz) and $J_{H\text{-}5,H\text{-}6}$ (10.4 Hz) indicated the *trans* relationship from H-1 to H-6, and from H-5 to H-6, while the small coupling constants of $J_{H\text{-}6,H\text{-}7}$ (4.0 Hz) suggested H-7 as *β*-oriented. A molecular modeling study based on no NOE correlation from H-1 to H_3-14 was used to determine the *β*-oriented Me-14. Finally, compound **1** was 6-*epi*-oplopanone.

Compound **2**, obtained as an optically active colorless oil with $[\alpha]_D^{20}$ +20 (*c* 0.1, $CHCl_3$), was assigned a molecular formula $C_{15}H_{26}O_3$ as analyzed from a pseudomolecular ion at *m/z* 277.1779 $[M + Na]^+$ (calcd. 277.1774) in its positive HRESIMS, indicative of three degrees of unsaturation. Its IR spectrum showed absorptions for hydroxy (3392 cm^{-1}) and ketone (1704 cm^{-1}) groups. A spectroscopic analogy of **2** with **1** indicated that compound **2** was an oplopanane-type sesquiterpenoid. The significant variations of **1** and **2** in their ^1H NMR spectra were the disappearance of methylene signals of H_2-2 (δ_H 1.90/1.42) in **1** and the appearance of a multiplet at δ_H 4.10 in **2**. These changes could be explained by the presence of a hydroxy group at C-2 in compound **2**, which was further elucidated from an HMBC experiment. In confirmation of the relative configuration, **2** gave a 2-monoacetate (**2a**) (Table 2) after overnight treatment with Ac_2O/Py (Sect. 3). As in **2a**, the coupling constants $J_{1,6} = 12.4$ Hz, $J_{1,2} = 9.2$ Hz, $J_{5,6} = 2.4$ Hz, and $J_{6,7} = 8.9$ Hz allowed the placement of H-5, H-6, and H-7 on α-orientation, and H-1 and OH-2 on α-orientation. The NOE correlations of H_3-14 with H-2/H-6, and H-5 with H-2/H-7 were used to determine H_3-14 as *β*-oriented. Thus, the structure of **2** was established as 5,7-*diepi*-2α-hydroxyoplopanone.



1 5αH, 7βH, $R_1 = R_2 = H$, $R_3 = O$
2 5βH, 7βH, $R_1 = OH$, $R_2 = H$, $R_3 = O$
2a 5βH, 7βH, $R_1 = OAc$, $R_2 = H$, $R_3 = O$
3, 4 5αH, 7αH, $R_1 = R_2 = H$, $R_3 = H, OH$
3a, 4a 5αH, 7αH, $R_1 = R_2 = H$, $R_3 = H, OAc$
5 5αH, 7αH, $R_1 = R_2 = H$, $R_3 = O$



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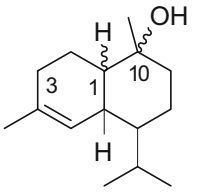

7 1βH, 10βOH
8 1αH, 10αOH

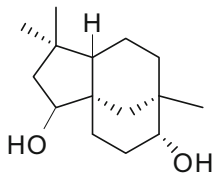

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Fig. 1 Molecular structures of sesquiterpenoids **1**−**9**

Table 1 NMR spectroscopic data for compound **1** in $CDCl_3$

Position	δ_H (J in Hz)	δ_C	Position	δ_H (J in Hz)	δ_C
1	2.07, ddd (6.8, 12.0, 12.0)	52.5 (d)	**8a**	1.55, m	23.0 (t)
			8b	1.01, dd (3.2, 13.6)	
2a	1.90, m	24.7 (t)	**9a**	1.77, dt (3.2, 12.4)	42.2 (t)
2b	1.42, m		**9b**	1.40, m	
3a	1.94, dt (2.8, 6.0)	27.5 (t)	**10**		73.2 (s)
3b	1.58, m				
4		212.3 (s)	**11**	1.67, m	29.2 (d)
5	3.12, ddd (3.2, 10.4, 10.4)	50.5 (d)	**12 and 13**	0.78, d (7.2)	15.8 (q)
				0.88, d (7.2)	21.3 (q)
6	1.35, ddd (4.0, 10.4, 12.0)	49.1 (d)	**14**	1.09, s	19.4 (q)
7	1.59, m	42.7 (d)	**15**	2.15, s	31.5 (q)

Table 2 NMR spectroscopic data for compounds **2**, **2a**, and **3** in $CDCl_3$

Position	**2**		**2a**		**3**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	1.50, m	60.4 (d)	1.75, dd (9.2, 12.4)	59.9 (d)	1.42, dt (4.8, 11.6)	57.5 (d)
2a	4.10, m	72.2 (d)	5.08, ddd (5.6, 8.8, 9.2)	74.0 (d)	1.78, dt (4.8, 12.4)	25.4 (t)
2b					1.18, m	
3a	1.82, m	36.9 (t)	2.08, m	35.8 (t)	1.75, m	22.5 (t)
3b	1.82, m		1.93, m		1.58, m	
4		210.9 (s)		210.0 (s)	3.98, q (6.4)	68.6 (d)
5	1.75, m	42.2 (d)	2.79, ddd (2.4, 8.0, 10.0)	44.1 (d)	1.72, m	48.9 (d)
6	2.73, m	52.6 (d)	1.86, ddd (2.4, 8.9, 12.4)	53.2 (d)	1.33, m	44.6 (d)
7	1.03, m	49.5 (d)	1.15, m	49.7 (d)	1.18, m	50.1 (d)
8a	1.51, m	22.6	1.58, m	22.3	1.62, m	23.1
8b	1.51, m	(t)	1.11, m	(t)	1.07, m	(t)
9a	1.34, m	41.5 (t)	1.77, m	41.0 (t)	1.73, m	41.8 (t)
9b	1.34, m		1.38, m		1.37, m	
10		73.4 (s)		72.0 (s)		73.0 (s)
11	1.30, m	28.7 (d)	1.38, m	29.0 (d)	1.91, m	28.1 (d)
12 and 13	0.61, d (6.8)	21.7 (q)	0.66, d (6.8)	21.9 (q)	0.89, d (8.4)	15.6 (q)
	0.83, d (6.8)	15.4 (q)	0.89, d (6.8)	15.4 (q)	0.93, d (7.2)	21.8 (q)
14	1.21, s	20.5 (q)	1.26, s	21.0 (q)	1.17, s	20.1 (q)
15	2.15, s	29.8 (q)	2.20, s	30.1 (q)	1.18, d (6.4)	23.1 (q)
C=O				171.3 (s)		
Me			2.04, s	21.3 (q)		

Compounds **3** and **4**, both isolated as optically active white floc with $[\alpha]_D^{20}$ −17 (*c* 0.1, $CHCl_3$) and $[\alpha]_D^{20}$ −27 (*c* 0.1, $CHCl_3$), respectively, possessed the same molecular formula of $C_{15}H_{28}O_2$ based on the positive HRESIMS data at *m/z* 258.2422 and 258.2428, respectively ($[M + NH_4]^+$, calcd. 258.2428). Their IR peaks at 3398 and 3352 cm^{-1} suggested the presence of hydroxy groups. Their ^{13}C NMR spectra were similar to those of **1**, with the exception that the carbonyl carbon at δ_C 212.3 in **1** was replaced by hydroxy-bearing methine carbons at δ_C 68.6 and 69.7 in **3** and **4**, respectively. The replacements of the C-4 ketone by secondary hydroxy group were supported by the presence of a quartet at δ_H 3.98 (1H, $J = 6.4$ Hz, assigned to H-4) of **3** and a doublet of quartet at δ_H 4.00 (1H, $J = 4.0$, 6.4 Hz, assigned to H-4) for **4** in the ^1H NMR spectrum, which were confirmed from HMBC correlations from H-4 to C-3,

C-5, C-6, and C-15. The structures of **3** and **4** were thus deduced as epimers of 4,10-dihydroxyoplopanane. The relative configurations of **3** and **4** were finalized by comparing their spectroscopic features with those of **1** and NOE experiment. The large coupling constants of $J_{1,6} = 11.6$ Hz in **3/4** and **3a/4a** (acetate of **3/4**, Sect. 3 and Tables 2, 3) were used to assign H-1 and H-6 as α- and β-orientation, respectively. Irradiation of H-4 enhanced signals for H-6 and H-11 in **3a** (acetate of **3**) and **4** allowed H-5 and H-7 as α-orientated. Efforts on the determination of the absolute configurations at C-4 in compounds **3** and **4** by using Mosher method failed. Therefore the structures of **3** and **4** were elucidated as depicted and named oplopananol and 4-*epi*-oplopananol, respectively.

On the basis of NMR, MS, optical rotation data and comparison with literature values, the known sesquiterpenoids were elucidated as oplopanone (**5**) [11], taiwaninone A (**6**) [12], T-muurolol (**7**) [13], α-cadinol (**8**) [14], and clovane-2β,9α-diol (**9**) [15]. Naturally occurring oplopanane sesquiterpenoids are rarely reported [16, 17]. Literature searching showed that there were no more than 20 such type sesquiterpenoids reported up to now, distributed among the families of Alismataceae [16, 17], Araliaceae [18], Araceae [19], Asteraceae [20], Chloranthaceae [21], Cyperaceae [22], Magnoliaceae [23], Meliaceae [24], Schisandraceae [25], Salicaceae [26], and Zingiberaceae [27]. In this study, six oplopananes (**1**–**6**), including four new (**1**–**4**) and one 3,5-*seco*-oplopanane (**6**), were discovered from the rhizomes of *H. occulta*. In addition three new oplopananes (**2a**–**4a**) were also obtained by chemical transformation. These results indicated that *H. occulta* was a rich source of novel natural products.

3 Experimental Section

3.1 General

Optical rotations were recorded on a 241 polarimeter (Perkin-Elmer). Infrared (IR) spectra were obtained with a FTS 165-IR instrument (Bio-Rad, USA). NMR spectra were acquired on a Varian INOVA-400 FT-NMR spectrometer (USA). HRESIMS were measured on a Bruker APEX II spectrometer. Sephadex LH-20 (Amersham Biosciences) and silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd) were used for column chromatography (CC), whereas TLC analyses were carried out with glass plates pre-coated with silica gel and the spots were visualized by spraying with 98 % H_2SO_4/EtOH in (5/95, v/v)

Table 3 NMR spectroscopic data for compounds **3a**, **4**, and **4a** in $CDCl_3$

Position	**3a**		**4**		**4a**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	1.38, m	57.6 (d)	1.44, dt (4.0, 12.8)	57.9 (d)	1.43, dt (4.8, 11.6)	57.7 (d)
2a	1.70, m	25.4 (t)	1.77, m	26.0 (t)	1.74, m	26.0 (t)
2b	1.20, m		1.08, m		1.74, m	
3a	1.86, m	24.4 (t)	1.80, m	23.6 (t)	1.80, m	24.2 (t)
3b	1.55, m		1.13, m		1.53, m	
4	4.98, q (6.4)	73.1 (d)	4.00, dq (4.0, 6.4)	69.7 (d)	5.06, m	72.7 (d)
5	1.38, m	46.9 (d)	2.05, m	48.7 (d)	2.12, m	45.2 (d)
6	1.14, m	45.1 (d)	0.93, m	46.2 (d)	0.98, m	45.9 (d)
7	1.22, m	50.0 (d)	1.21, m	50.1 (d)	1.18, m	49.9 (d)
8a	1.59, m	23.3 (t)	1.63, ddt (3.2, 4.0, 13.6)	23.4 (t)	1.63, dq (4.0, 13.6)	23.2 (t)
8b	1.03, dt (3.6, 11.6)		1.06, m		1.08, m	
9a	1.76, dt (3.6, 12.4)	41.9 (t)	1.76, m	41.9 (t)	1.77, m	41.9 (t)
9b	1.35, m		1.37, dt (4.0, 13.2)		1.36, dt (4.0, 12.8)	
10		73.0 (s)		73.0 (s)		73.0 (s)
11	1.86, m	28.2 (d)	1.93, m (2.4)	28.5 (d)	2.09, m	28.1 (d)
12 and 13	0.72, d (7.2)	22.0 (q)	0.72, d (6.8)	15.7 (q)	0.75, d (6.8)	15.7 (q)
	0.90, d (6.8)	15.5 (q)	0.94, d (6.8)	21.9 (q)	0.94, d (6.8)	22.0 (q)
14	1.12, s	19.9 (q)	1.14, s	20.1 (q)	1.14, s	20.1 (q)
15	1.19, d (6.4)	19.6 (q)	1.12, d (6.4)	17.0 (q)	1.16, d (6.4)	13.8 (q)
16		170.9 (s)				170.6 (s)
17	2.01, s	21.3 (q)			2.01, s	21.5 (q)

followed by heating. All solvents used were analytical grade.

3.2 Plant Materials

The rhizomes of *H. occulta* Lours (Araceae), collected from Guangxi in China, were purchased from Lanzhou Fuxinghou Herbal Medicines Ltd. Co. in February 2007. The materials were identified by Dr. Huan-Yang Qi at Lanzhou Institute of Chemical Physics (LICP), and a voucher specimen (ZY2007H001) was deposited at the herbarium of LICP.

3.3 Extraction and Isolation

The air-dried rhizomes (13.0 kg) of *H. occulta* were powdered and extracted with 88 % ethanol/water (v/v) at 60 °C (12 h × 3). After dried in vacuum, the residue (410 g) was suspended in water (1.5 L) and applied to a liquid–liquid partitioning against petroleum ether (PE), EtOAc, and *n*-BuOH (each 1.0 L × 3) continuously. The dried PE part (257 g) was chromatographed over silica gel (1.5 kg), using gradient PE/acetone (v/v, from 80:1 to 1:1, each about 8.0 L) to yield eleven fractions (A1–A11). Fraction A2 (55 g) was subjected to silica gel CC eluting with $CHCl_3$/PE gradient system to afford compound **8** (18.2 mg). Fraction A3 (21 g) was purified over silica gel with PE/$CHCl_3$ (v/v, 1:1) to afford **7** (4.5 mg). Fraction A5 (34 g) was fractionated consecutively over silica gel and Sephadex LH-20 ($CHCl_3$/MeOH, 1:1, v/v) to yield compound **5** (4.5 mg). Fraction A6 (12 g) was chromatographed on a silica gel column eluting with PE/acetone (v/v, 10:1, 8:1, 5:1, 3:1, and 1:1) to afford compound **1** (5.1 mg). Fraction A7 (15 g) was fractionated consecutively over silica gel with PE/acetone (8:1) and Sephadex LH-20 ($CHCl_3$/MeOH, 1:1, v/v) to yield **2** (7.8 mg), **3** (23.1 mg), **4** (17.7 mg), **6** (17.8 mg), and **9** (2.1 mg).

*3.3.1 7-Epi-oplopanone (**1**)*

Colorless oil; $[\alpha]_D^{20}$–54 (*c* 0.07, $CHCl_3$); IR (neat) ν_{max} 3382, 2926, 2857, 1705, 1458, 1383, 1119, 1094, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 1); HRESIMS *m/z* $[M + NH_4]^+$ 256.2272 (calcd for $C_{15}H_{30}O_2N$, 256.2271).

*3.3.2 5,7-Diepi-2α-hydroxyoplopanone (**2**)*

Colorless oil; $[\alpha]_D^{20}$ +20 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3392, 2955, 2935, 2871, 1704, 1460, 1380, 1365, 1173, 1121, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 2); HRESIMS *m/z* $[M + Na]^+$ 277.1779 (calcd for $C_{15}H_{26}O_3Na$, 277.1774).

*3.3.3 Oplopananol (**3**)*

White floc; $[\alpha]_D^{20}$–17 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3398, 2959, 2933, 1461, 1370, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 2); HRESIMS *m/z* $[M + NH_4]^+$ 258.2422 (calcd for $C_{15}H_{32}O_2N$, 258.2428).

*3.3.4 4-Epi-oplopananol (**4**)*

White floc; $[\alpha]_D^{20}$ –27 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3352, 2956, 2924, 2856, 1571, 1458, 1421, 1365, 1128, 1062, 944 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 3); HRESIMS *m/z* $[M + NH_4]^+$ 258.2428 (calcd for $C_{15}H_{32}O_2N$, 258.2428).

3.4 Acetylation of **2** to **4**

A solution of compounds in a mixture of acetic anhydride–pyridine (1:1) were stirred fully and settled at 25 °C for 12 h. After concentration and storage in *vacuo* compounds **2a**, **3a**, and **4a** were obtained and identified.

*3.4.1 5,7-Diepi-2α-acetoxyoplopanone (**2a**)*

Colorless oil; $[\alpha]_D^{20}$ +7 (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3449, 2934, 2871, 1734, 1712, 1370, 1247, 1044, 968 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 2); HRESIMS *m/z* $[M + Na]^+$ 319.1883 (calcd for $C_{17}H_{28}O_4Na$, 319.1880).

*3.4.2 4-Acetoxyoplopananol (**3a**)*

Colorless oil; $[\alpha]_D^{20}$–41 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max}(log ε) 246 (1.56) nm; IR (neat) ν_{max} 3423, 2960, 2935, 2892, 1736, 1458, 1375, 1247, 1134, 1033, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 3); HRESIMS *m/z* $[M + Na]^+$ 305.2091 (calcd for $C_{17}H_{30}O_3Na$, 305.2087).

*3.4.3 4-Epi-acetoxyoplopananol (**4a**)*

White floc; $[\alpha]_D^{20}$ –10 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max}(log ε) 246 (1.48) nm; IR (neat) ν_{max} 3420, 2858, 2935, 2872, 1732, 1374, 1248, 1126, 1035, 953 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) (Table 3); HRESIMS *m/z* $[M + Na]^+$ 305.2093 (calcd for $C_{17}H_{30}O_3Na$, 305.2087).

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing financial interest.

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